



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<b>(51) International Patent Classification <sup>6</sup> :</b>  <b>B01D 9/00</b>	<b>A1</b>	<b>(11) International Publication Number:</b> <b>WO 98/23350</b>  <b>(43) International Publication Date:</b> 4 June 1998 (04.06.98)
<b>(21) International Application Number:</b> PCT/GB97/02927  <b>(22) International Filing Date:</b> 23 October 1997 (23.10.97)  <b>(30) Priority Data:</b> 9624615.2                      26 November 1996 (26.11.96)      GB  <b>(71) Applicant (for all designated States except US):</b> ZENECA LIMITED [GB/GB]; 15 Stanhope Gate, London W1Y 6LN (GB).  <b>(72) Inventors; and</b> <b>(75) Inventors/Applicants (for US only):</b> WOOD, William, Malcolm, Logan [GB/GB]; Process Studies Group, Zeneca Huddersfield Works, Leeds Road, P.O. Box A38, Huddersfield, West Yorkshire HD2 1FF (GB). GEORGE, Neil [GB/GB]; Process Studies Group, Zeneca Huddersfield Works, Leeds Road, P.O. Box A38, Huddersfield, West Yorkshire HD2 1FF (GB). DAWSON, Stephen [GB/GB]; Process Studies Group, Zeneca Huddersfield Works, Leeds Road, P.O. Box A38, Huddersfield, West Yorkshire HD2 1FF (GB).  <b>(74) Agents:</b> HOUGHTON, Malcolm, John et al.; Zeneca Agrochemicals, Intellectual Property Dept., Jealott's Hill Research Station, P.O. Box 3538, Bracknell, Berkshire RG42 6YA (GB).		<b>(81) Designated States:</b> AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).  <b>Published</b> <i>With international search report.</i>
<b>(54) Title:</b> CRYSTALLISATION PROCESS  <b>(57) Abstract</b>  A process for preparing a crystal suspension of an organic compound which has a $\Delta H/RT$ value greater than 10, the process comprising dispersing a melt of the organic compound in a liquid dispersion medium to form an emulsion, cooling the emulsion below the melting point of the organic compound and subjecting the emulsion to ultrasonic vibration.		

***FOR THE PURPOSES OF INFORMATION ONLY***

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

<b>AL</b>	Albania	<b>ES</b>	Spain	<b>LS</b>	Lesotho	<b>SI</b>	Slovenia
<b>AM</b>	Armenia	<b>FI</b>	Finland	<b>LT</b>	Lithuania	<b>SK</b>	Slovakia
<b>AT</b>	Austria	<b>FR</b>	France	<b>LU</b>	Luxembourg	<b>SN</b>	Senegal
<b>AU</b>	Australia	<b>GA</b>	Gabon	<b>LV</b>	Latvia	<b>SZ</b>	Swaziland
<b>AZ</b>	Azerbaijan	<b>GB</b>	United Kingdom	<b>MC</b>	Monaco	<b>TD</b>	Chad
<b>BA</b>	Bosnia and Herzegovina	<b>GE</b>	Georgia	<b>MD</b>	Republic of Moldova	<b>TG</b>	Togo
<b>BB</b>	Barbados	<b>GH</b>	Ghana	<b>MG</b>	Madagascar	<b>TJ</b>	Tajikistan
<b>BE</b>	Belgium	<b>GN</b>	Guinea	<b>MK</b>	The former Yugoslav Republic of Macedonia	<b>TM</b>	Turkmenistan
<b>BF</b>	Burkina Faso	<b>GR</b>	Greece			<b>TR</b>	Turkey
<b>BG</b>	Bulgaria	<b>HU</b>	Hungary	<b>ML</b>	Mali	<b>TT</b>	Trinidad and Tobago
<b>BJ</b>	Benin	<b>IE</b>	Ireland	<b>MN</b>	Mongolia	<b>UA</b>	Ukraine
<b>BR</b>	Brazil	<b>IL</b>	Israel	<b>MR</b>	Mauritania	<b>UG</b>	Uganda
<b>BY</b>	Belarus	<b>IS</b>	Iceland	<b>MW</b>	Malawi	<b>US</b>	United States of America
<b>CA</b>	Canada	<b>IT</b>	Italy	<b>MX</b>	Mexico	<b>UZ</b>	Uzbekistan
<b>CF</b>	Central African Republic	<b>JP</b>	Japan	<b>NE</b>	Niger	<b>VN</b>	Viet Nam
<b>CG</b>	Congo	<b>KE</b>	Kenya	<b>NL</b>	Netherlands	<b>YU</b>	Yugoslavia
<b>CH</b>	Switzerland	<b>KG</b>	Kyrgyzstan	<b>NO</b>	Norway	<b>ZW</b>	Zimbabwe
<b>CI</b>	Côte d'Ivoire	<b>KP</b>	Democratic People's Republic of Korea	<b>NZ</b>	New Zealand		
<b>CM</b>	Cameroon		Republic of Korea	<b>PL</b>	Poland		
<b>CN</b>	China	<b>KR</b>	Republic of Korea	<b>PT</b>	Portugal		
<b>CU</b>	Cuba	<b>KZ</b>	Kazakstan	<b>RO</b>	Romania		
<b>CZ</b>	Czech Republic	<b>LC</b>	Saint Lucia	<b>RU</b>	Russian Federation		
<b>DE</b>	Germany	<b>LI</b>	Liechtenstein	<b>SD</b>	Sudan		
<b>DK</b>	Denmark	<b>LK</b>	Sri Lanka	<b>SE</b>	Sweden		
<b>EE</b>	Estonia	<b>LR</b>	Liberia	<b>SG</b>	Singapore		

### CRYSTALLISATION PROCESS

This invention relates to a crystallisation process and, in particular, to a process for producing a crystalline suspension of an organic compound in a liquid medium.

In the agrochemical industry, pesticides are often supplied in the form of suspension concentrates. These comprise a largely insoluble, particulate active ingredient suspended in a liquid medium, usually an aqueous medium. They are commonly prepared by ball or bead milling a millbase consisting of the active ingredient, liquid medium and one or more dispersing agents, and then formulated with additives and a volume-adjusting amount of the liquid medium. Additives may include, for example, antissettling or suspension agents, preservatives, antifoams, antifreezes and biological adjuvants.

It is important to the industry to be able to provide fluid, storage stable concentrates without the need for stirred storage vessels or the use of thickeners to maintain the solid particles in suspension. A key factor in obtaining a physically stable product is the particle size of the suspended solid. Normally, the smaller the particle size, the more stable is the suspension.

Milling is a common technique for reducing the particle size of a suspended solid, but may not always produce the best results, and, because it generates considerable heat, may not always be appropriate, for example, where the active ingredient is a low melting solid.

An alternative technique is to crystallise the solid from an emulsion of the melted solid, or a solution of it, in the liquid medium. For example, it is known from EP-A-0221465 to prepare suspensions by dispersing a melt above its solidification temperature in an aqueous phase and allowing the melt to solidify by cooling it below its crystallisation temperature. It is also known from DE-A-2551841 and DE-A-2900268 that a melt can be dispersed in an aqueous phase having a temperature below the solidification temperature of the melt. Dispersions of this type are produced using high speed stirrers or rotor-stator machines. The disadvantage of these processes is that they tend to give only coarse dispersions with short shelf lives, although finer dispersions may be obtained if, as described in EP-A-0399266, the initial emulsion is subjected to an additional homogenisation step.

In these emulsions, the melt is suspended in the aqueous phase in the form of droplets. If the droplets crystallise rapidly, the crystal size distribution will be the same as the original droplet size within the emulsion. Therefore, in theory, it should be possible to

generate finer and more stable dispersions by reducing the droplet size. However, as the droplet size decreases, crystallisation becomes slower. Furthermore, the solubility of the droplet in the continuous phase increases with decreasing droplet size, due to higher pressures within the droplet. The effect of this is that the continuous phase concentration can  
5 rise to a level where it becomes supersaturated relative to the crystalline form, with the result that nucleation and crystal growth occurs in the continuous phase. As nucleation rates tend to be slow in the continuous phase, large crystals are generated which bear no resemblance to the original droplets. This is clearly undesirable if fine dispersions are to be obtained.

The use of ultrasound for crystallising melts and solutions is well known. For  
10 example, a process for the crystallisation of adipic acid from aqueous solution is known from US-A-5471001. It is also known to use ultrasonics for preparing emulsions and fine droplet dispersions (see, for example, WO-A-94/20072). It has now been found that ultrasound can be used to generate finer particle size, more stable dispersions from emulsions.

Thus, according to the present invention there is provided a process for preparing a  
15 crystalline suspension of an organic compound which has a  $\Delta H/RT$  value greater than 10, the process comprising dispersing a melt of the organic compound in a liquid dispersion medium to form an emulsion, cooling the emulsion below the melting point of the organic compound and subjecting the emulsion to ultrasonic vibration.

The value  $\Delta H/RT$  is a well understood expression which means the enthalpy (heat) of  
20 fusion of a compound ( $\Delta H$  in  $\text{kJmol}^{-1}$ ) at the normal melting point of the compound divided by the molar gas constant ( $R$ , where  $R$  is  $8.31451 \text{ Jmol}^{-1}\text{K}^{-1}$ ) and the melting point of the compound measured on the absolute or Kelvin scale (in  $^{\circ}\text{K}$ ). Thus, for example, the  $\Delta H/RT$  value of octadecane, which has a melting point of  $28.2^{\circ}\text{C}$  and a heat of fusion of  $61.39 \text{ kJmol}^{-1}$  (see the *CRC Handbook of Chemistry and Physics*, [1996-1997], 77<sup>th</sup> Edition,  
25 6-138) is calculated as follows:

$$61.39/8.31451 \times 10^{-3} \times (28.2 + 273.16) = 24.5$$

The heat of fusion of a compound ( $\Delta H$ ) may be measured by differential scanning calorimetry. A suitable method is described by McNaughton, J.L. and Mortimer, C.T. in  
IRS: Physical Chemistry Series 2, Butterworth, London 1975, Vol 10; subsequently reprinted  
30 by Perkin-Elmer Corp. Norwalk, CT, USA.

The invention is of particular interest in the formulation of low melting agrochemicals, especially pesticides such as fungicides, insecticides and herbicides, as suspension concentrates. It will be evident, however, that the process is equally applicable to the preparation of a crystalline suspension of any other low melting organic compound.

5 Where the crystalline suspension is to be stored for long periods at ambient temperature, it is desirable that the organic compound has a melting point above 20°C and, preferably, above 30°C. However, the melting point should not be higher than the boiling point of the chosen liquid medium dispersion medium at its operating pressure. This pressure will be as high as it is reasonably practicable or economical to pressurize the apparatus being used. Thus,  
10 where the liquid medium is water, as will normally be the case, the organic compound may have a melting point of from 20°C to 200°C, the upper temperature being possible where the apparatus is pressurized to around 14bar. Suitably the organic compound will have a melting point of from 20°C to 120°C for example, from 30°C to 100°C and, typically, from 40°C to 90°C.

15 The liquid dispersion medium, which may be any suitable liquid, for example, water or an agriculturally acceptable organic solvent that is benign to living tissue, will ideally have a crystallisation point of at least 10°C, suitably 20°C, below the crystallisation point of the organic compound, and a boiling point of at least the same order as the melting point of the organic compound, and preferably at least 5°C above the melting point of the organic  
20 compound, for example, from 10°C to 30°C above. Of most interest, however, are those suspensions where the liquid dispersion medium is an aqueous medium and where the emulsion formed is an oil-in-water emulsion.

Conveniently, the organic compound is melted and heated to a temperature slightly above its melting point, for example 5°C to 10°C above, and added to the liquid dispersion  
25 medium heated to approximately the same temperature as the melt, ie within 5°C or so. Alternatively, the organic compound may be added to the liquid medium at a temperature above or below the melting point of the organic compound, for example prior to heating to the melt temperature, and the temperature adjusted until the organic compound has melted.

Depending on the crystallisation properties of the organic compound, it may also be  
30 possible to add the melt to the liquid medium at a temperature below the melting point of the organic compound without further heating.

The concentration of the organic compound in the liquid dispersion medium will be up to 60% w/w, normally from 20% w/w to 60% w/w, for example, from 30% w/w to 50% w/w, and typically around 40% w/w.

The liquid medium may contain additives, for example one or more dispersing agents, or other additives of the type normally used in the preparation of crystalline suspensions and which are well documented in the literature.

The liquid medium containing the melt or solution is vigorously agitated using, for example, a high shear mixer or homogeniser or a combination of these, to generate the desired droplet size of the suspended organic compound. Generally, droplet sizes of less than 10µm (mean diameter), for example between 1µm and 10µm and preferably between 1µm and 5µm, are required, but the present invention is also applicable to sub-micron droplets.

The emulsion so formed is cooled, preferably as rapidly as possible, to a temperature below the melting point of the organic compound, suitably to a temperature of from 1°C to 80°C, depending on the melting point of the organic compound and the nature of the liquid dispersion medium. For a compound with a melting point of, for instance, 70°C to 80°C and where the liquid dispersion medium is water, the emulsion may be cooled from 30°C to 70°C, for example from 50°C to 60°C, below the melting point of the organic compound. For a compound with a melting point of, for instance, 20°C to 40°C, the emulsion may be cooled from 1°C to 20°C, for example from 3°C to 10°C, below the melting point of the organic compound. After cooling, ultrasonic vibration is applied until crystallisation has progressed to an acceptable degree.

Any suitable source of ultrasonic vibration may be used. A half-inch diameter (12.7mm) ultrasonic probe operating at 20kHz and a power input of 100watts has been found convenient, but there will be many other commercially available devices equally suitable.

The invention is of particular interest for preparing a crystalline suspension of the fungicide methyl (*E*)-2-{2-[6-(trifluoromethyl)pyridin-2-yloxymethyl]phenyl}-3-methoxyacrylate (EP-A-0278595; compound No. 177, Table I) and a eutectic mixture of this compound with the fungicide azoxystrobin (methyl (*E*)-2-{2-[6-(2-cyanophenoxy)pyrimidin-4-yloxy]phenyl}-3-methoxyacrylate). It may, however, be used for other low melting agrochemical compounds and, indeed, for any other low melting organic compound with a suitable  $\Delta H/RT$  value, such as a C<sub>16</sub> to C<sub>20</sub> saturated aliphatic hydrocarbon, for example,

hexadecane, octadecane, nonadecane or eicosane, or a C<sub>12</sub> to C<sub>16</sub> saturated fatty acid, for example, tetradecanoic acid.

The invention is illustrated by the following Examples in which the compound A is methyl (*E*)-2-{2-[6-(trifluoromethyl)pyridin-2-yloxy]methyl]phenyl}-3-methoxyacrylate  
5 having a melting point 76°C and a  $\Delta H/RT$  value of 10.55, and *Morwet* D425\* which is an anionic naphthalene sulphonic acid - formaldehyde condensate, and *Atlox* 4913\* which is a non-ionic polymethacrylate, are both used as dispersing agents. The following abbreviations are used throughout:

g = grammes	%w/w = percent weight by weight	°C = degrees centigrade
mm = millimetres	µm = micrometres	kHz = kiloHertz
w = watts	mp = melting point	$\Delta H$ = heat of fusion (kJmol <sup>-1</sup> )
R = molar gas constant (8.31451 Jmol <sup>-1</sup> k <sup>-1</sup> )		T = temperature in degrees Kelvin

10

### EXAMPLE 1

A melt of compound A (100g) at 80°C was added to water (150g) at 80°C containing *Morwet* D425 (0.3%w/w of the total formulation) and *Atlox* 4913 (4.8% w/w of the total formulation). The water with added melt was agitated vigorously using a *Silverson* high  
15 shear mixer. A dispersion containing droplets of 5-10µm (average diameter) was generated. The dispersion was cooled rapidly (within 5 minutes) to 20°C in a jacketed vessel. A 12mm ultrasonic probe (obtained from *Heat Systems Ultrasonics Inc*) operating at 20kHz and at a power input of 100w, was submersed in the dispersion and sonication applied for 30 minutes. The rate of crystallisation was followed by microscopic observation under cross-  
20 polars.

By comparison with a dispersion prepared and processed in the same way, but without sonication, the use of ultrasound was shown to increase the nucleation rate within the dispersed melt droplets. This was apparent from the following observations:

---

\* The names *Morwet* and *Atlox* are registered trade marks

1. The time to crystallise the whole dispersion was reduced from 1 hour to 10 minutes using ultrasound.
2. The crystal size distribution of the sonicated dispersion corresponded more closely to the droplet size distribution of the original emulsion.
3. Scanning Electron Microscopy confirmed that all the droplets of the sonicated dispersion had crystallised. The resulting particles were roughly spherical and comprised mainly individual intergrown crystals. Although some droplets of the non-sonicated dispersion crystallised, the crystal number per droplet was lower and some large, flat crystals were formed.

#### EXAMPLE 2

A dispersion was prepared in exactly the same way as in Example 1, except that the water with added melt was homogenised using a *Niro-Soavi* valve homogeniser set at 50bar, instead of being agitated using a *Silverson* high shear mixer. This generated a melt dispersion with droplets of the order of 3µm. Sonication produced a fluid dispersion of 3µm diameter spherical crystals which appeared to be porous (high surface area).

By comparison, a dispersion prepared and processed in exactly the same way, but without sonication, produced a solidified dispersion of flat crystals that were much larger than the original droplets. These had crystallised from the continuous aqueous phase.

#### EXAMPLE 3

A eutectic mixture of compound A 75% w/w and azoxystrobin (mp 121°C, ΔH/RT 11.64) 25% w/w was prepared and melted at 95°C. This mixture was homogenised (*Soavi* high pressure homogeniser) at 50bar with 2.4% w/w *Morwet* D425 and 4.8% w/w *Atlox* 4913 to form droplets of around 2µm in size. On cooling to 40°C crystallisation occurred in the continuous phase in the absence of sonication. In the presence of sonication the droplets could be seen to crystallise within minutes, generating diamond shaped crystals in equal numbers to the droplets.

#### EXAMPLES 4 TO 7

Hexadecane (C<sub>16</sub>H<sub>34</sub>, mp 20°C), Octadecane (C<sub>18</sub>H<sub>38</sub>, mp 28°C, ΔH/RT 24.52),



Nonadecane ( $C_{19}H_{40}$ , mp  $32^{\circ}\text{C}$ ,  $\Delta H/RT = 18.06$ ) and Eicoasane ( $C_{20}H_{42}$ , mp  $36^{\circ}\text{C}$   $\Delta H/RT = 27.13$ ).

These compounds were all emulsified (at 20% w/w oil phase) with *Tween* 20 (2% w/w) above their melting points using a Silverson mixer. This gave droplets of the order of 5-10 $\mu\text{m}$ . On cooling to  $10^{\circ}\text{C}$ ,  $20^{\circ}\text{C}$ ,  $29^{\circ}\text{C}$ , and  $30^{\circ}\text{C}$ , respectively, all crystallised slowly in droplets. On sonication, however, the droplets crystallised within 90sec for hexadecane, 15sec for octadecane, 25sec for nonadecane and 30sec for eicosane. Clearly, the nucleation rate of these droplets was greatly enhanced, indicating that smaller crystalline droplets could be produced.

10

#### EXAMPLE 8

Tetradecanoic Acid ( $C_{14}H_{28}O_2$ , mp  $54^{\circ}\text{C}$ ,  $\Delta H/RT = 16.69$ )

A 4% w/w dispersion was emulsified with 0.4% *Span* 20 and 1% w/w *Mowiol* 8-88 using a Silverson mixer. These 5 $\mu\text{m}$  droplets also crystallised rapidly on cooling to  $46^{\circ}\text{C}$  but it was noticeable under the microscope that in the presence of sonication the crystallisation rate within the droplets increased (crystallised within 10sec).

15

CLAIMS

1. A process for preparing a crystal suspension of an organic compound which has a  $\Delta H/RT$  value greater than 10, the process comprising dispersing a melt of the organic  
5 compound in a liquid dispersion medium to form an emulsion, cooling the emulsion below the melting point of the organic compound and subjecting the emulsion to ultrasonic vibration.
2. A process according to claim 1 in which the organic compound has a melting point  
10 above 20°C.
3. A process according to claim 1 in which the organic compound has a melting point between 30°C and 100°C.
- 15 4. A process according to claim 1 in which the liquid dispersion medium has a crystallisation point of at least 10°C below the melting point of the organic compound and a boiling point of at least the same order as the melting point of the organic compound.
- 20 5. A process according to claim 1 in which the liquid dispersion medium is an aqueous medium.
6. A process according to claim 3 in which the emulsion formed is an oil-in-water  
25 emulsion.
7. A process according to claim 1 in which the melt is added to the liquid dispersion medium while the liquid dispersion medium is at approximately the same temperature as the melt.
- 30 8. A process according to claim 1 in which the melt of the organic compound is dispersed in the liquid dispersion medium using a high shear mixer.

9. A process according to claim 1 in which the melt of the organic compound is dispersed in the liquid dispersion medium using a homogeniser.
- 5 10. A process according to claim 1 in which the organic compound is dispersed in the liquid dispersion medium in the form of droplets having a mean diameter of from between 1 $\mu$ m to 10 $\mu$ m.
11. A process according to claim 1 in which the emulsion is rapidly cooled to a  
10 temperature of from 10°C to 80°C below the melting point of the organic compound.
12. A process according to any one of the preceding claims in which the organic compound is methyl (*E*)-2-[2-[6-(trifluoromethyl)pyridin-2-yloxymethyl]phenyl]-3-methoxyacrylate.

# INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 97/02927

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 B01D9/00

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 B01D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	PATENT ABSTRACTS OF JAPAN vol. 13, no. 553, 8 December 1989 & JP 01 228502 A (KAO CORP.), 12 September 1989, see abstract ---	1-6
A	EP 0 278 595 A (IMPERIAL CHEMICAL INDUSTRIES PLC) 17 August 1988 cited in the application see tables 1, NO.177 ---	1,12
A	WO 94 20072 A (K.WESTESEN ET AL.) 15 September 1994 cited in the application see claim 1 -----	1

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

### \* Special categories of cited documents :

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

- \*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- \*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- \*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- \*G\* document member of the same patent family

Date of the actual completion of the international search

4 February 1998

Date of mailing of the international search report

25.02.98

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
Fax: (+31-70) 340-3016

Authorized officer

Bertram, H

# INTERNATIONAL SEARCH REPORT

information on patent family members

International Application No

PCT/GB 97/02927

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 278595 A	17-08-88	AU 615890 B	17-10-91
		AU 1066088 A	11-08-88
		CN 1030749 A,B	01-02-89
		DE 3875748 A	17-12-92
		DE 3889345 D	01-06-94
		DE 3889345 T	01-09-94
		DK 66888 A	10-08-88
		EG 19678 A	30-09-95
		EP 0472224 A	26-02-92
		ES 2052696 T	16-07-94
		ES 2053258 T	16-07-94
		GB 2201152 A,B	24-08-88
		GB 2235454 A,B	06-03-91
		GB 2235455 A,B	06-03-91
		GB 2235456 A,B	06-03-91
		IE 60730 B	10-08-94
		IL 85122 A	29-12-94
		IL 98742 A	18-06-96
		IL 98743 A	16-10-96
		IL 107289 A	10-06-97
		JP 2559130 B	04-12-96
		JP 63216848 A	09-09-88
		JP 9002906 A	07-01-97
		KR 9613832 B	10-10-96
		KR 9605513 B	25-04-96
		US 5438059 A	01-08-95
		US 5021581 A	04-06-91
-----			
WO 9420072 A	15-09-94	CA 2091152 A	06-09-94
		AU 676279 B	06-03-97
		AU 6225394 A	26-09-94
		EP 0687172 A	20-12-95
		FI 954143 A	19-10-95
		JP 8507515 T	13-08-96
		NO 953461 A	06-11-95
		NZ 262541 A	24-04-97
-----			